



## Intranasal Rhinitis Agents Therapeutic Class Review (TCR)

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## FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
<b>Nasal Corticosteroids</b>		
beclomethasone (Beconase AQ®) <sup>1</sup>	GlaxoSmithKline	<ul style="list-style-type: none"> <li>▪ Relief of symptoms of seasonal or perennial allergic rhinitis and non-allergic (vasomotor) rhinitis in adults and children 6 years of age and older</li> <li>▪ Prevention of recurrence of nasal polyps following surgical removal</li> </ul>
beclomethasone (Qnasl®) <sup>2</sup>	Teva Specialty	<ul style="list-style-type: none"> <li>▪ Treatment of nasal symptoms associated with seasonal and perennial allergic rhinitis in adults and adolescents 4 years of age and older</li> </ul>
budesonide OTC (Rhinocort® Allergy) <sup>3</sup>	Johnson & Johnson	<ul style="list-style-type: none"> <li>▪ Temporary relief of hay fever or other upper respiratory allergies, including nasal congestion, runny nose, sneezing, and itchy nose, in adults and children 6 years of age and older</li> </ul>
ciclesonide (Omnaris®) <sup>4</sup>	Covis	<ul style="list-style-type: none"> <li>▪ Treatment of nasal symptoms of seasonal allergic rhinitis in adults and children 6 years of age and older</li> <li>▪ Treatment of nasal symptoms of perennial allergic rhinitis in adults and children 12 years of age and older</li> </ul>
ciclesonide (Zetonna®) <sup>5</sup>	Covis	<ul style="list-style-type: none"> <li>▪ Treatment of symptoms associated with seasonal and perennial allergic rhinitis in adults and adolescents 12 years of age and older</li> </ul>
flunisolide <sup>6</sup>	generic	<ul style="list-style-type: none"> <li>▪ Relief of nasal symptoms of seasonal or perennial allergic rhinitis in adults and children 6 years of age and older</li> </ul>
fluticasone furoate OTC (Flonase® Sensimist™ Allergy Relief) <sup>7</sup>	GlaxoSmithKline	<ul style="list-style-type: none"> <li>▪ Temporary relief of symptoms of hay fever or other upper respiratory allergies, including nasal congestion, runny nose, sneezing, itchy nose, and itchy, watery eyes in adults and children 2 years of age and older</li> </ul>
fluticasone propionate <sup>8</sup>	generic	<ul style="list-style-type: none"> <li>▪ Management of nasal symptoms of perennial non-allergic rhinitis in adults and children 4 years of age and older</li> </ul>
fluticasone propionate OTC (Flonase Allergy Relief®, Clarispray®) <sup>9,10</sup>	GlaxoSmithKline, Bayer, generic	<ul style="list-style-type: none"> <li>▪ Temporary relief of symptoms of hay fever or other upper respiratory allergies, including nasal congestion, runny nose, sneezing, itchy nose, and itchy/watery eyes, in adults and children 4 years of age and older</li> </ul>
fluticasone propionate (Ticanase™) <sup>11</sup>	PureTek, Shoreline	<ul style="list-style-type: none"> <li>▪ Treatment of nasal symptoms of perennial non-allergic rhinitis in adults and children 4 years of age and older</li> </ul>
fluticasone propionate (Xhance™) <sup>12</sup>	OptiNose	<ul style="list-style-type: none"> <li>▪ Treatment of nasal polyps in patients 18 years of age or older</li> </ul>
mometasone (Nasonex®) <sup>13</sup>	Schering, generic	<ul style="list-style-type: none"> <li>▪ Treatment of nasal symptoms of seasonal and perennial allergic rhinitis in adults and children 2 years of age and older</li> <li>▪ Treatment of nasal congestion associated with seasonal allergic rhinitis in adults and children 2 years of age and older</li> <li>▪ Prophylaxis of nasal symptoms of seasonal allergic rhinitis in adults and children 12 years of age and older</li> <li>▪ Treatment of nasal polyps in patients 18 years of age and older</li> </ul>
mometasone (Sinuva™) <sup>14</sup>	Intersect ENT	<ul style="list-style-type: none"> <li>▪ Corticosteroid-eluting implant indicated for the treatment of nasal polyps in patients ≥ 18 years of age who have had ethmoid sinus surgery</li> </ul>
triamcinolone OTC (Nasacort® Allergy 24HR) <sup>15</sup>	Chattem Consumer, generic	<ul style="list-style-type: none"> <li>▪ Temporary relief of symptoms of hay fever or other upper respiratory allergies, including nasal congestion, runny nose, sneezing, and itchy nose, in adults and children 2 years of age and older</li> </ul>

### FDA-Approved Indications (continued)

Drug	Manufacturer	Indication(s)
<b>Intranasal Antihistamines</b>		
azelastine <sup>16</sup>	generic	<ul style="list-style-type: none"> <li>Relief of the symptoms of seasonal and perennial allergic rhinitis in patients 12 years of age and older</li> </ul>
azelastine (Astepro®) <sup>17</sup>	Meda, generic	<ul style="list-style-type: none"> <li>Relief of symptoms of seasonal allergic rhinitis in adults and children 2 years of age and older and perennial allergic rhinitis in adults and children 6 months of age and older</li> </ul>
olopatadine (Patanase™) <sup>18</sup>	Alcon, generic	<ul style="list-style-type: none"> <li>Relief of symptoms of seasonal allergic rhinitis in adults and children 6 years of age and older</li> </ul>
<b>Intranasal Corticosteroid and Antihistamine Combinations</b>		
azelastine / fluticasone propionate (Dymista®) <sup>19</sup>	Meda	<ul style="list-style-type: none"> <li>Relief of symptoms of seasonal allergic rhinitis in patients 6 years of age and older who require treatment with both agents for symptomatic relief</li> </ul>
azelastine/ fluticasone propionate/ saline nasal wash* (Ticalast™ kit) <sup>20</sup>	Shoreline	<ul style="list-style-type: none"> <li>Relief of symptoms of seasonal allergic rhinitis in patients 6 years of age and older who require treatment with both agents for symptomatic relief</li> </ul>
<b>Others</b>		
hypromellose (Alzair™) <sup>21</sup>	Hudson Scientific	<ul style="list-style-type: none"> <li>Reduces the symptoms of allergic rhinitis</li> </ul>
ipratropium nasal spray 0.03% <sup>22</sup>	generic	<ul style="list-style-type: none"> <li>Symptomatic relief of rhinorrhea associated with allergic and nonallergic perennial rhinitis in adults and children 6 years of age and older</li> </ul>
ipratropium nasal spray 0.06% <sup>23</sup>	generic	<ul style="list-style-type: none"> <li>Symptomatic relief of rhinorrhea associated with the common cold or seasonal allergic rhinitis in adults and children 5 years of age and older</li> </ul>

\* Products packaged as kits are discussed in the FDA Indications and Dosages sections, and components are addressed in the Pharmacology section. For other information regarding these products, please refer to the primary component throughout the text.

Triamcinolone nasal spray (Nasacort Allergy 24HR), fluticasone furoate (Flonase Sensimist Allergy Relief), fluticasone propionate nasal spray (Flonase Allergy Relief, Clarispray Nasal Allergy), and budesonide nasal spray (Rhinocort Allergy) are available without a prescription.

Regeneron Pharmaceuticals' dupilumab (Dupixent®) is an interleukin-4 receptor alpha antagonist indicated as an add-on to maintenance therapy in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis (CRSwNP).<sup>24</sup> It is supplied as a 300 mg/2 mL solution in a single dose pre-filled syringe with a needle shield. The recommended dose for this indication is 300 mg given subcutaneously every other week. The patients may self-inject the dose after proper training. Due to the route of administration of this medication, it will not be detailed in this therapeutic class review.

## OVERVIEW

Allergic rhinitis (AR) is a constellation of symptoms affecting 7.7% of adults and 7.2% of children in the United States in 2018<sup>25</sup> The condition is characterized by sneezing, itching of the eyes, nose, and palate, rhinorrhea, and nasal obstruction. It is often associated with post-nasal drip, cough, irritability, and fatigue. Symptoms develop when patients inhale airborne antigens to which they have previously been exposed and have made antibodies. The antibodies bind to receptors on mast cells in respiratory mucosa and to basophils in peripheral blood. Mast cells release pre-formed and granule-associated chemical mediators. In addition, mast cells generate other inflammatory mediators and cytokines, which lead to nasal inflammation and, with continued allergen exposure, chronic symptoms.<sup>26</sup>

Perennial allergic rhinitis is an IgE-mediated reaction to allergens with little or no seasonal variation. The condition is persistent, chronic, and generally less severe than seasonal allergic rhinitis. Allergic rhinitis is driven by the mucosal infiltration and action on plasma cells, mast cells, and eosinophils as part of an allergic response.

Vasomotor rhinitis, or irritant rhinitis, is a condition of unknown origin, which seems to be aggravated by fumes, odors, temperature, atmospheric changes, smoke, and other irritants. This form of rhinitis (generally a condition diagnosed in adults) causes year-round symptoms that include congestion and headache.

In 2017, the American Academy of Allergy, Asthma and Immunology (AAAAI) released a focused evidence-based guideline update for Seasonal Allergic Rhinitis (SAR).<sup>27</sup> These guidelines are intended to provide guidance for health providers for the treatment of both adult and adolescent patients ( $\geq 12$  to 15 years of age) with allergic rhinitis. Pharmacological therapy may include intranasal and oral antihistamines decongestants and corticosteroids. Other therapies include intranasal cromolyn, intranasal anticholinergics, and leukotriene receptor antagonists (LTRAs). When specific monotherapy management is being considered, intranasal corticosteroids are more effective than LTRAs. If a patient is not adequately controlled on an intranasal corticosteroid or has moderate to severe symptoms, addition of an antihistamine may be considered, preferably an intranasal antihistamine agent versus an oral antihistamine product. The guidelines do not specify one agent over another.<sup>28</sup>

According to the 2008 American Academy of Allergy, Asthma and Immunology (AAAAI) practice parameter for the management of rhinitis, the selection of pharmacotherapy for a patient depends on multiple factors, including the type of rhinitis present (e.g., allergic, non-allergic, mixed, episodic), most prominent symptoms, severity, and patient age. Response to previous treatment, patient and family preferences, compliance with therapy, and cost are additional factors that enter the management decision. Rhinitis medication management frequently requires a step-up approach, if therapy is inadequate, or a step-down approach, if symptom relief is achieved or maximized with other approaches, including avoidance measures.<sup>29</sup> Second generation oral antihistamines are generally preferred over first generation oral antihistamines for treatment of allergic rhinitis because they have less of a tendency to cause sedation, performance impairment, and/or anticholinergic adverse effects. Intranasal antihistamines have demonstrated efficacy that is equal to or superior to oral second generation antihistamines in the treatment of seasonal allergic rhinitis. These agents are also effective and have been associated with a clinically significant effect on nasal congestion for nonallergic rhinitis, but are generally less effective than intranasal corticosteroids for treatment of allergic rhinitis. Combination therapy with intranasal corticosteroids may provide an added benefit.

The Institute for Clinical Systems Improvement's (ICSI) Diagnosis and Treatment of Respiratory Illness in Children and Adults 2017 guidelines state that non-infectious rhinitis can be either allergic or non-allergic.<sup>30</sup> Symptomatic treatment includes education on antigen avoidance and medication therapy. As with the chronic use of any medications, special consideration of risk and benefit may need to be given to the elderly, fragile patients, pregnant women, athletes, and children. The following medications are recommended for use in patients with allergic rhinitis: intranasal corticosteroids, intranasal and oral antihistamines, decongestants, cromolyn, anticholinergics, leukotriene receptor antagonists, and combination intranasal antihistamines/corticosteroids. Intranasal corticosteroids have a long onset of action, but are the first-line recommendation for allergic rhinitis. Intranasal antihistamines have a shorter duration of action, they are considered not as effective as intranasal corticosteroids. Oral antihistamines control all symptoms of allergic rhinitis, except nasal congestion and are somewhat less effective than intranasal corticosteroids. Combination intranasal antihistamine/corticosteroids therapy is more effective in treating rhinitis symptoms, had shorter onset of action, and are not associated with increased adverse effects compared to either agent used alone. Chronic, obstructive, nasal symptoms secondary to nonallergic rhinitis can be managed with intranasal corticosteroids, antihistamine, or ipratropium bromide formulations, and oral decongestants. In addition to conservative treatment measures (e.g., increased water intake, nasal saline irrigation, decreased caffeine and alcohol intake, increased humidity), intranasal corticosteroids are recommended when medical treatment is necessary for symptomatic, non-purulent, chronic postnasal drip. For rhinorrhea due to nonallergic rhinitis, intranasal corticosteroids, intranasal ipratropium, or nasal saline can be used if patients are unable to avoid offending irritants.

The 2015 American Academy of Otolaryngology – Head and Neck Surgery Clinical Practice Guideline for Allergic Rhinitis recommends the use of intranasal steroids and oral antihistamines as first-line treatment for allergic rhinitis in adults and children over 2 years of age.<sup>31</sup> The panel issued a strong recommendation for use of intranasal steroids in patients whose quality of life is affected by allergic rhinitis, as well as for oral second generation antihistamines for patients with sneezing and itching as their primary complaints. Clinicians may offer intranasal antihistamines as second-line therapy for patients with seasonal, perennial, or episodic allergic rhinitis, after failure of intranasal steroids or oral antihistamines. There may be specific patients in whom an intranasal antihistamine would be an appropriate first-line treatment. The guideline also recommends combination therapy in patients who have had an inadequate response to monotherapy. The most effective addition to intranasal steroid therapy is an intranasal antihistamine.

## **PHARMACOLOGY<sup>32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55</sup>**

Following topical administration, corticosteroids produce anti-inflammatory and vasoconstrictor effects. They gain entry into the cell cytoplasm and interact with glucocorticoid receptors. The receptor complex undergoes a conformational change, becoming active prior to entering the cell nucleus. Gene expression is hypothesized to be the principal mechanism of modulating the inflammatory state. Direct effects may be a reduction in cytokine-induced production of pro-inflammatory mediators. Clinical benefits observed with corticosteroids can be attributed to wide-ranging suppressive effects on the immune system and anti-inflammatory mediator production.<sup>56</sup> Fluticasone propionate (Xhance) and mometasone (Sinuva) are specifically for the treatment of nasal polyps in adult patients. However, the exact mechanism of action is unknown for this indication. Fluticasone propionate (Xhance) uses a bi-directional exhalation delivery system (EDS) designed to deliver drug higher and deeper in the nasal

passages, compared to traditional nasal sprays.<sup>57</sup> However, clinical studies have not been conducted comparing effectiveness on nasal congestion, nasal obstruction symptoms, or nasal polyp grade of fluticasone propionate EDS (Xhance) with other nasal corticosteroids used to treat nasal polyps.

Azelastine (Astepro, Dymista) is a phthalazine derivative, which exhibits histamine (H<sub>1</sub>) receptor antagonist activity. Azelastine also demonstrates inhibitory effects on the release of inflammatory mediators from mast cells.<sup>58</sup> The drug is 100 to 1,000 times more potent than cromolyn sodium, theophylline, astemizole, and verapamil in mast cell mediator release inhibition.<sup>59</sup> Olopatadine (Patanase) is an antihistamine with selective H<sub>1</sub> receptor antagonist activity.

Ipratropium bromide (Atrovent) is an anticholinergic agent that blocks cholinergic receptors and reflex-mediated hypersecretion from nasal glands. Ipratropium bromide is a quaternary amine, which minimally crosses nasal and gastrointestinal membranes and the blood-brain barrier, resulting in a reduction of systemic anticholinergic effects.

Saline (sodium chloride 0.9%) nasal wash, a component of select product kits, is used to moisturize and lubricate dry nasal passages via a gentle mist. Large volume low pressure irrigation of nasal and sinus cavities also may be performed.

Hypromellose (Alzair) particles absorb moisture from the nasal mucosa and swell to create a protective gel-like barrier in the nasal tract. This gel barrier prevents allergens from making contact with the mucosa, thus stopping cell degranulation and the release of histamines from within the body.

## PHARMACOKINETICS<sup>60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78</sup>

Due to the route of administration, intranasal agents used to treat allergic rhinitis have very poor bioavailability. Pharmacokinetic information is limited and often extrapolated from other dosage forms.

## CONTRAINDICATIONS/WARNINGS<sup>79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100,101</sup>

There are no specific contraindications for any of the intranasal corticosteroids, azelastine (Astepro, Dymista), or olopatadine (Patanase). Hypersensitivity to any of the ingredients in the nasal spray, inhaler, or device contraindicates its use.

### Nasal Corticosteroids

If a topical corticosteroid replaces a systemic corticosteroid, signs of adrenal insufficiency may appear. In susceptible individuals, systemic corticosteroid effects, such as hypercorticism and adrenal suppression, may appear. If this occurs, nasal corticosteroid therapy should be slowly discontinued. However, a 6-week clinical trial reported that serum cortisol weighted mean values were similar in patients treated with beclomethasone dipropionate 320 mcg once daily and placebo.<sup>102</sup>

Patients with immunosuppression are more susceptible to infections than healthy patients. Some patients who use immunosuppressive doses of corticosteroids can acquire more serious and even fatal responses to disseminated infections.

Patients using any of the nasal corticosteroids should be monitored periodically for adverse effects on the nasal mucosa. Instances of epistaxis, nasal ulceration, nasal septa perforations, impaired wound

healing, and *Candida albicans* have all been reported. Avoid use in patients with recent nasal ulcers, nasal surgery, or nasal trauma.

The use of nasal corticosteroids could potentiate the development of posterior subcapsular cataracts or glaucoma. Patients should be monitored closely if they have an increase in intraocular pressure, cataracts, glaucoma, or experience any vision change (e.g., blurred vision). **Consider referral to an ophthalmologist in patients who develop ocular symptoms.** Central serous chorioretinopathy has occurred with select agents in this class in postmarketing reports.

## Intranasal Antihistamines

Due to somnolence, patients should be advised to assess their individual responses to azelastine (Astepro, Dymista) nasal spray or olopatadine (Patanase) nasal spray before engaging in any activity requiring mental alertness, such as driving a car or operating machinery. Patients should be advised that the concurrent use of azelastine nasal spray or olopatadine nasal spray with alcohol or other central nervous system (CNS) depressants may lead to additional reductions in alertness and impairment of CNS performance and should be avoided. Epistaxis and nasal ulceration have been reported in placebo-controlled clinical trials with olopatadine (Patanase).

Ipratropium (Atrovent) nasal spray should be used with caution in patients with narrow-angle glaucoma, prostatic hyperplasia, or bladder neck obstruction due to anticholinergic properties of ipratropium.

## DRUG INTERACTIONS<sup>103,104,105,106,107,108,109,110,111,112,113,114,115,116,117,118,119,120,121,122</sup>

Fluticasone propionate (Flonase Allergy Relief, Dymista, Ticanase), fluticasone furoate (Flonase Sensimist), and mometasone (Nasonex) are substrates of cytochrome P450 3A4. Co-administration of fluticasone nasal spray (Flonase Allergy Relief, Flonase Sensimist, Dymista, Ticanase) and protease inhibitors is not recommended. A drug interaction study in healthy patients demonstrated that ritonavir can increase plasma fluticasone levels resulting in significantly reduced serum cortisol concentrations.

Drug-drug interaction studies were not conducted for the following nasal sprays: olopatadine (Patanase), ipratropium (Atrovent), or mometasone (Sinuva). Based on *in vitro* metabolism data, olopatadine drug interactions involving P450 inhibition are not expected. Evaluation of mometasone (Sinuva) with other commonly used nasal drugs did not exhibit any unusual adverse effects.

## ADVERSE EFFECTS<sup>123,124,125,126,127,128,129,130,131,132,133,134,135,136,137,138,139,140,141,142,143,144</sup>

### Nasal Corticosteroids

Drug	Pharyngitis	Epistaxis	Cough	Nasal Irritation/Discomfort
beclomethasone (Beconase AQ)	nr	< 3	nr	24
beclomethasone (Qnasl)	nr	1.9	nr	5.2
budesonide (Rhinocort Allergy) n=1,526; up to 400 mcg	4	8	2	2
ciclesonide (Omnaris) n=546; up to 200 mcg	3.7	4.9	nr	> 1
ciclesonide (Zetonna)	≥ 2	2.9	≥ 2	3.2
flunisolide	< 3–9	3–9	< 3	13–44
fluticasone furoate (Flonase Sensimist Allergy Relief) n=768; 110 mcg	2	6	nr	1
fluticasone propionate (Flonase Allergy Relief, Ticanase) n=782; 200 mcg	7.8	6.9	3.8	3.2
fluticasone propionate (Xhance)	≥ 2	≥ 2	< 1	≥ 2
mometasone (Nasonex) n=2,103; 200 mcg	12	11	7	reported
mometasone (Sinuva) n=254; 200 mcg	3	6	nr	nr
triamcinolone (Nasacort Allergy 24HR) n=857; 220 mcg	5.1	2.7	2.1	nr

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. nr = not reported.

Overall, intranasal corticosteroids are well tolerated in adult and pediatric patients. Serious adverse effects that may result in discontinuation include epistaxis and nasal septal perforation.

A study evaluated whether use of fluticasone propionate, mometasone furoate, or beclomethasone dipropionate for treatment of rhinitis produced an increase in intraocular pressure.<sup>145</sup> The authors conducted a comparative, double-blind, experimental, prospective, longitudinal study in which 360 patients were randomized into 1 of 4 groups. Ninety patients were given a placebo (control group). The other 270 were divided into 3 groups of 90 patients each. A different nasal corticosteroid was given to each group. All patients had intraocular pressure measured by Goldman's tonometry at 3 weeks, 6 weeks, 3 months, 6 months, and 1 year after using placebo or intranasal steroid. Fluticasone propionate, mometasone furoate, and beclomethasone dipropionate caused variations in intraocular pressure, but the variations were within normal limits.

## Intranasal Antihistamines

Drug	Bitter Taste/ Taste Disturbance	Headache	Myalgia	Nasal Burning	Somnolence	Weight Increase
azelastine n=391 placebo n=353	19.7 (0.6)	14.8 (12.7)	1.5 (0)	4.1 (1.7)	11.5 (5.4)	2 (0)
azelastine 0.1% (Astepro) n=146; vehicle n=138	7 (2)	3 (< 1)	nr	1 (0)	2 (0)	nr
azelastine 0.15% (Astepro) n=523; vehicle n=523	6 (1)	nr	nr	3 (2)	< 1 (< 1)	nr
olopatadine (Patanase) n=587 vehicle n=593	12.8 (0.8)	4.4 (4)	nr	nr	0.9 (0.3)	nr
azelastine / fluticasone propionate (Dymista)	4 (< 1)	2 (1)	nr	nr	< 1	nr

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. Incidences for placebo group are in parentheses. nr = not reported

## Others

Drug	Nasal Dryness	Nasal Irritation	Epistaxis	Dry Mouth/Throat
ipratropium nasal 0.03% n=356 perennial allergic rhinitis	5.1	2	9	< 2
ipratropium nasal 0.06% n=352 common cold	4.8	Nasal burning < 1	8.2	1.4

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive.

## Monitoring

In children, intranasal corticosteroids should be used at the lowest effective dose, and the Food and Drug Administration (FDA) recommends that height be routinely monitored due to potential reduction in growth velocity.<sup>146,147</sup>

## **SPECIAL POPULATIONS**<sup>148,149,150,151,152,153,154,155,156,157,158,159,160,161,162,163,164,165,166,167,168,169</sup>

### **Pediatrics**

With the exception of mometasone (Sinuva) and fluticasone propionate (Xhance), which are approved for patients  $\geq 18$  years, all other agents in this class are approved in pediatrics. Please refer to the FDA-Approved Indications chart or to the individual package inserts for specific age criteria.

Controlled clinical studies have shown that intranasal corticosteroids may cause a reduction in growth velocity in pediatric patients; however, the impact on final adult height is unknown.<sup>170</sup> Over-the-counter (OTC) use of an intranasal corticosteroid should be limited to  $\leq 2$  months in children 2 to 11 years of age. A prescriber should be consulted for use beyond 2 months.

### **Pregnancy**

Azelastine (Astepro, Dymista), olopatadine (Patanase), and all of the intranasal corticosteroids, except budesonide, are Pregnancy Category C. Data available for fluticasone propionate (Xhance) does not suggest there is an association for risks to the fetus nor adverse developmental outcomes. Ipratropium (Atrovent) and budesonide are Pregnancy Category B. There are no randomized clinical studies available that evaluate mometasone (Sinuva) in pregnant women.

Labeling for ciclesonide (Omnaris) was updated to comply with the Pregnancy and Lactation Labeling Rule (PLLR). There are no data for use in pregnant women to assess a drug-associated risk to the mother or fetus; however, there is low systemic drug exposure with the recommended dose.

### **Other Considerations**

Reduced liver function may affect the elimination of corticosteroids. The relevance of this finding to intranasal administration of corticosteroids has not been established. Ipratropium and olopatadine (Patanase) have not been studied in patients with hepatic impairment. Ipratropium (Atrovent) has not been studied in patients with renal impairment.

## DOSAGES<sup>171,172,173,174,175,176,177,178,179,180,181,182,183,184,185,186,187,188,189,190,191</sup>

Drug	Adults (> 12 years)*	Children (< 12 years)	Availability
<b>Nasal Corticosteroids</b>			
beclomethasone (Beconase AQ)	1–2 sprays in each nostril twice daily	(≥ 6 years) 1–2 sprays in each nostril twice daily	42 mcg/spray; 25 gm–180 sprays
beclomethasone (Qnasl)	2 sprays in each nostril once daily (Qnasl 80 mcg) (maximum 4 sprays per day)	(4–11 years) 1 spray in each nostril daily (Qnasl 40 mcg) (maximum 2 sprays per day)	40 mcg/spray; 6.8 gm–60 actuations; 80 mcg/spray; 10.6 gm–120 actuations
budesonide OTC (Rhinocort Allergy)	2 sprays in each nostril daily	(≥ 6 years) 1–2 sprays in each nostril daily; A physician should be consulted for use beyond 2 months	32 mcg/spray; 5 mL – 60 sprays
ciclesonide (Omnaris)	2 sprays in each nostril daily	(≥ 6 years) 2 sprays in each nostril daily	50 mcg/spray; 12.5 gm–120 sprays
ciclesonide (Zetonna)	1 spray in each nostril daily	--	37 mcg/spray; 6.1 gm–60 actuations
flunisolide	2 sprays in each nostril twice daily up to 8 sprays in each nostril daily	(≥ 6 years) 1 spray in each nostril 3 times daily or 2 sprays in each nostril twice daily	25 mcg aerosol; 25 mL–200 doses
fluticasone furoate (Flonase Sensimist Allergy Relief)	Week 1: use 2 sprays in each nostril once daily; Week 2 through 6 months: use 1–2 sprays in each nostril once daily, as needed for symptoms; A physician should be consulted for use beyond 6 months	(2–11 years) 1 spray in each nostril daily; A physician should be consulted for use beyond 2 months	27.5 mcg/spray; 9.9 mL–60 sprays and 15.8 mL–120 sprays
fluticasone propionate	2 sprays in each nostril daily or 1 spray in each nostril twice daily	(≥ 4 years) 1 spray in each nostril daily; May increase to a max of 2 sprays per nostril for severe symptoms	50 mcg/spray; 16 gm–120 sprays
fluticasone propionate (Ticanase)	fluticasone propionate: 2 sprays in each nostril daily or 1 spray in each nostril twice daily saline nasal spray: use only as directed	(≥ 4 years) fluticasone propionate: 1 spray in each nostril daily; May increase to a max of 2 sprays per nostril if not adequately responding saline nasal spray: use only as directed	Kit containing fluticasone propionate nasal spray (50 mcg/spray; 16 gm – 120 actuations) and saline nasal spray (6 fl oz)
fluticasone propionate OTC (Flonase Allergy Relief)	Week 1: 2 sprays in each nostril once daily; Week 2 through 6 months: 1 – 2 sprays in each nostril once daily as needed	(4–11 years) 1 spray in each nostril daily	50 mcg/spray; 16 gm–120 sprays*
fluticasone propionate (Xhance) <sup>†</sup>	1 spray in each nostril twice daily	(≥ 18 years) 2 sprays in each nostril daily	93 mcg/spray; 16 mL- 120 sprays

**Dosages (continued)**

<b>Drug</b>	<b>Adults (&gt; 12 years)*</b>	<b>Children (&lt; 12 years)</b>	<b>Availability</b>
<b>Nasal Corticosteroids (continued)</b>			
mometasone (Nasonex)	2 sprays in each nostril daily Adults 18 years and older: Nasal polyps: 2 sprays in each nostril twice daily	(≥ 2 years) 1 spray in each nostril daily	50 mcg/spray; 17 gm–120 sprays
mometasone (Sinuva)	Adults 18 years of age and older: 1,350 mcg of mometasone furoate can be delivered over 90 days	--	Implant system contains 1,350 mcg of mometasone furoate within a sterile delivery system
triamcinolone OTC (Nasacort® Allergy 24 HR)	2 sprays in each nostril daily	(2–5 years) 1 spray in each nostril daily (6–12 years) 1–2 sprays in each nostril daily A physician should be consulted for use beyond 2 months	55 mcg/spray; 16.5 gm–120 sprays
<b>Intranasal Antihistamines</b>			
azelastine	Seasonal allergic rhinitis: 1–2 sprays in each nostril twice daily Vasomotor rhinitis: 2 sprays in each nostril twice daily	Seasonal allergic rhinitis: (≥ 5 years) 1 spray in each nostril twice daily	137 mcg/spray; 30 mL–200 sprays
azelastine (Astepro)	Seasonal allergic rhinitis: 1–2 sprays in each nostril twice daily (azelastine 0.1% and 0.15%) or 2 sprays in each nostril once daily (Astepro 0.15%) Perennial allergic rhinitis: 2 sprays in each nostril twice daily (Astepro 0.15%)	Seasonal allergic rhinitis: (2–5 years) 1 spray in each nostril twice daily (azelastine 0.1%) (6–11 years) 1 spray in each nostril twice daily (azelastine 0.1% and 0.15%) Perennial allergic rhinitis: (6 months–5 years) 1 spray in each nostril twice daily (azelastine 0.1%) (6–11 years) 1 spray in each nostril twice daily (azelastine 0.1% and 0.15%)	137 mcg/spray; 30 mL–200 sprays (azelastine 0.1%) 205.5 mcg/spray; 30 mL–200 sprays (Astepro 0.15%); Discard once spray capacity has been reached even if not empty
olopatadine (Patanase)	2 sprays in each nostril twice daily	(≥ 6 years) 1 spray in each nostril twice daily	0.6% (665 mcg/100 mL spray); 30.5 gm–240 sprays

## Dosages (continued)

Drug	Adults (> 12 years)*	Children (< 12 years)	Availability
<b>Intranasal Corticosteroid and Antihistamine Combinations</b>			
azelastine / fluticasone propionate (Dymista®)	1 spray in each nostril twice daily	(≥ 6 years) 1 spray in each nostril twice daily	137 mcg/ 50 mcg per spray 23 gm–120 sprays
azelastine / fluticasone propionate / saline (Ticalast kit)‡	Spray: 1 spray in each nostril twice daily Nasal wash: as directed by physician	Spray: (≥ 6 years) 1 spray in each nostril twice daily Nasal wash: as directed by physician	Kit containing Spray: 137 mcg/ 50 mcg per spray 23 gm–120 sprays Saline nasal wash: 120 mL
<b>Others</b>			
hypromellose (Alzair)	Firmly squeeze a 6-inch plume at least 3 times daily (minimum) or as needed	Gently squeeze a 2-inch plume at least 3 times daily (minimum) or as needed	Nasal powder spray bottle
ipratropium 0.03%	Perennial allergic rhinitis: 2 sprays in each nostril 2 or 3 times daily	(≥ 6 years) 2 sprays in each nostril 2 or 3 times daily	21 mcg/spray 30 mL–345 sprays
ipratropium 0.06%	Seasonal allergic rhinitis: 2 sprays in each nostril 4 times daily	(≥ 5 years) 2 sprays in each nostril 4 times daily	42 mcg/spray 15 mL–165 sprays
	Common cold: 2 sprays in each nostril 3 or 4 times daily not to exceed 4 days	(≥ 5 years) 2 sprays in each nostril 3 times daily not to exceed 4 days	

For fluticasone, some patients 12 years of age and older have found as-needed usage of 200 mcg once daily (2 sprays in each nostril) to be an effective treatment of seasonal allergic rhinitis.

For all products listed above, the pump must be primed prior to first use and again if stored unused after a certain period of time (which are product specific). Consult package inserts.

\* One formulation of fluticasone propionate spray is available under the trade name ClariSpray™ and another is under the trade name Aller-Flo™.

† Xhance uses a bi-directional exhalation delivery system (EDS) to dispense the dose of fluticasone propionate. To administer Xhance, the tip of the nosepiece is inserted deep into 1 nostril to form a tight seal between the nosepiece and the nostril. Next, the patient blows into the mouthpiece, while simultaneously actuating the spray pump.<sup>192</sup>

‡ Ticalast saline nasal wash includes 3 nozzle sizes — a large tip for large volume rinse of the nasal and sinus, a medium tip for a stronger stream, and a tip to deliver a gentle mist. To prevent pressure in the nose or ears, do not completely block nasal passage during use.

## CLINICAL TRIALS

### Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class and allergic rhinitis. Randomized, controlled, comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance. Many of the trials with agents in this class were performed in an open-label manner; introduction of bias must be considered when evaluating study findings.

Several agents in this class have demonstrated efficacy versus placebo.<sup>193,194,195,196,197,198,199,200,201,202,203,204,205,206,207,208</sup> Comparative trials regarding use for rhinitis are included in more detail below. There are no comparative trials for agents approved for the treatment of nasal polyps; however, efficacy has been demonstrated in placebo-controlled trials.<sup>209,210,211</sup>

### Seasonal Allergic Rhinitis

#### ***budesonide (Rhinocort) versus mometasone (Nasonex)***

In a double-blind, crossover design study, 38 patients with seasonal allergic rhinitis received treatment with spray formulations of placebo, budesonide 64 mcg, budesonide 256 mcg, and mometasone furoate 200 mcg.<sup>212</sup> Treatment was initiated for 3 days prior to allergen challenges and administered daily for 7 days while intranasal treatment continued. Active treatments reduced nasal symptoms and improved nasal peak inspiratory flow (PIF) ( $p < 0.001$  to  $0.05$ ). Budesonide caused dose-dependent improvements in evening symptoms, morning nasal PIF, and nasal PIF recorded 10 minutes after allergen challenge ( $p < 0.05$ ). Budesonide 256 mcg produced greater improvement than mometasone 200 mcg in nasal PIF 10 minutes after allergen challenge ( $p < 0.05$ ).

#### ***azelastine versus azelastine plus fexofenadine (Allegra®)***

In a 2-week, multicenter, double-blind trial, 334 patients with moderate-to-severe seasonal allergic rhinitis were randomized to 1 of 3 treatments: 1) azelastine 2 sprays per nostril twice daily, 2) azelastine 2 sprays per nostril twice daily and fexofenadine 60 mg twice daily, or 3) placebo given twice daily.<sup>213</sup> All patients were given a 1-week run-in with fexofenadine 60 mg twice daily. Patients who improved  $< 33\%$  were randomized to 1 of the 3 regimens. After 14 days of treatment, the azelastine and azelastine plus fexofenadine groups showed greater improvement in Total Nasal Symptom Score (TNSS) than placebo ( $p = 0.007$ ). Azelastine alone was as effective as azelastine plus fexofenadine.

### ***azelastine versus azelastine (Astepro)***

A randomized, double-blind, parallel-group study containing 835 patients with seasonal allergic rhinitis was performed comparing the efficacy of reformulated azelastine nasal spray (Astepro) to the original azelastine formulation (Astelin®) and determined if a dose-response relationship existed.<sup>214</sup> The patients were randomized into 6 groups: original azelastine nasal spray, 1 spray per nostril twice daily; reformulated azelastine, 1 spray per nostril twice daily; placebo nasal spray, 1 spray per nostril twice daily; original azelastine nasal spray, 2 sprays per nostril twice daily; reformulated azelastine nasal spray, 2 sprays per nostril twice daily; and placebo nasal spray, 2 sprays per nostril twice daily. The study concluded the original and reformulated azelastine products had comparable improvements in the 12-hour reflective TNSS in both dosages after 14 weeks. Patients treated with original ( $p \leq 0.01$ ) and reformulated azelastine ( $p \leq 0.001$ ) nasal spray groups at dosages of 2 sprays per nostril twice daily had a change in TNSS baseline that was statistically superior to placebo, 23.5%, 27.9%, and 15.4%, respectively. However, the original and reformulated azelastine nasal spray groups dosed at 1 spray per nostril were not statistically significant compared to placebo which was attributed to an abnormally high placebo response rate (19%). The study further determined a TNSS dose-response difference favoring the higher dosages existed. The incidence of adverse effects was low for both dosage formulations. Both azelastine groups reported bitter taste as the most common adverse effect, and nasal discomfort was more prevalent in the original azelastine product. Overall, the study's results indicated both formulations are effective in treating seasonal allergic rhinitis symptoms and a dose-response difference was present.

### ***azelastine versus fluticasone propionate***

In a double-blind, placebo-controlled, parallel-group trial, 610 patients ( $\geq 12$  years old) with moderate-to-severe SAR were randomized to receive azelastine (137 mcg/spray) or fluticasone propionate (50 mcg/spray), both given as 1 spray/nostril twice daily.<sup>215</sup> The primary efficacy measure was change from baseline in reflective TNSS (rTNSS) (morning and evening) over 14 days. Reflective total ocular symptom score (rTOSS), reflective total of seven symptom scores (rT7SS [nasal plus ocular symptoms]), and time to  $\geq 50\%$  reduction from baseline in these parameters were secondary measures. Both drugs reduced rTNSS from baseline by a similar degree (-3.25 versus -3.84;  $p=0.2014$ ). Patients experienced comparable improvement in rTOSS (-2.62 versus -2.17;  $p=0.2371$ ) and rT7SS (-5.83 versus -6.05;  $p=0.7820$ ). Fluticasone propionate was favored over azelastine in alleviating rhinorrhea (-1.15 versus -0.87;  $p=0.0433$ ), but azelastine showed comparable efficacy for all other nasal and ocular symptoms. There was no clinically or statistically significant difference between azelastine (-1.17) and fluticasone propionate (-1.43) for reduction in the overall rhinitis quality of life questionnaire score, although fluticasone propionate, but not azelastine, significantly differed from placebo. A similar proportion of patients in the azelastine and fluticasone propionate groups achieved a 50% reduction in rTNSS. However, more azelastine patients (53%) exhibited a 50% reduction in rTOSS by day 14 than FP patients (40%), and this endpoint occurred at least 3 days earlier with azelastine ( $p=0.028$ ).

### ***fluticasone furoate (Flonase Sensimist Allergy Relief) versus fluticasone propionate (Flonase)***

A randomized, placebo-controlled, double-blind, cross-over study was conducted in 360 patients with seasonal allergic rhinitis symptoms to compare the preferences for fluticasone furoate and fluticasone propionate nasal sprays after 1 week of treatment.<sup>216</sup> Patients were randomized to active treatment (fluticasone furoate 110 mcg or fluticasone propionate 200 mcg, followed by crossover treatment for 1 week each) or matched placebo sequence with a 1 week washout before crossover dosing. The

primary efficacy endpoints were measured by change from baseline during 1 week in daily rTNSS that assessed severity of rhinorrhea, nasal congestion, nasal itching, and sneezing. Patient preference was assessed at the end of the study by questionnaire. Both fluticasone furoate and fluticasone propionate each reduced the daily rTNSS compared with their respective placebos (least squares mean [SD] difference, -0.8 [0.24],  $p < 0.001$ , and -0.6 [0.24],  $p = 0.01$ , respectively). More patients ( $p < 0.001$ ) preferred fluticasone furoate to fluticasone propionate based on attributes of scent or odor (58% versus 27%), aftertaste (60% versus 18%), leaking out of the nose and down the throat (59% versus 21%), and mist gentleness (57% versus 26%). However, there were no statistically significant differences seen in preferences regarding ease of use, delivery method, or device comfort.

### ***olopatadine hydrochloride nasal spray 0.6% (Patanase) versus azelastine hydrochloride nasal spray 0.1% versus placebo***

A study was conducted as a phase 3, multicenter, randomized, double-blind, active and placebo-controlled parallel group study.<sup>217</sup> It included 544 individuals who were  $\geq 12$  years with a history of seasonal allergic rhinitis and verified allergy to a prevalent local allergen. Efficacy was assessed by changes in mean daily TNSS. Tolerability was evaluated based on adverse events, as well as nasal, physical, and cardiovascular parameters. Patients were randomly assigned olopatadine, azelastine, or placebo given as 2 sprays in each nostril twice daily for 16 days. The mean reductions from baseline in reflective TNSS were 26.8% with olopatadine, 29.9% with azelastine, and 18.4% with placebo ( $p = 0.003$ , for olopatadine versus placebo). The most commonly reported adverse effect of bitter taste was significantly lower with olopatadine than with azelastine (12.2% versus 19.7%, respectively;  $p = 0.05$ ). In conclusion, the TNSS percentage reduction was greater with olopatadine than placebo but not significantly different from azelastine. Both active treatments were well tolerated.

### ***olopatadine hydrochloride nasal spray 0.6% (Patanase) versus fluticasone propionate nasal spray 50 mcg (Flonase)***

A 2-week double-blind, randomized, 2-arm parallel-group, noninferiority trial was conducted comparing olopatadine nasal spray 0.6% (2 sprays per nostril twice daily) to fluticasone nasal spray 50 mcg (2 sprays per nostril once daily) for the treatment of seasonal allergic rhinitis.<sup>218</sup> Symptomatic patients ( $n = 130$ ) were equally divided between the 2 groups and required to record nasal and ocular symptoms twice daily throughout the study. The study found olopatadine nasal spray 0.6% provided a faster and greater onset of action compared to fluticasone nasal spray 50 mcg. However, at the end of the 2-week study, olopatadine nasal spray 0.6% compared to fluticasone nasal spray 50 mcg had no statistically significant difference in relief of seasonal allergic rhinitis symptoms with a mean reduction of 45.4% and 47.4%, respectively.

### ***azelastine / fluticasone propionate (Dymista) versus azelastine versus fluticasone versus placebo***

Adults and children, 12 years and older ( $n = 853$ ), with seasonal allergic rhinitis were enrolled in 3 randomized, double-blind, placebo- and active-controlled, parallel-group, trials.<sup>219</sup> Patients were randomized to 1 spray twice daily of azelastine/fluticasone propionate combination nasal spray, azelastine nasal spray, fluticasone propionate nasal spray, or vehicle placebo. In all 3 trials, combination therapy demonstrated statistically significant greater decreases in rTNSS (-5.6 versus -4.3 versus -4.7 versus -2.9, respectively;  $p \leq 0.002$  for all) and instantaneous TNSS (iTNS) (-5.2 versus -3.9 versus -4.5 versus -2.7, respectively;  $p < 0.001$  for all) as compared to azelastine hydrochloride and to fluticasone propionate, as well as to placebo.

## Perennial Allergic Rhinitis

### *ipratropium nasal spray 0.03% versus beclomethasone nasal spray (Beconase AQ)*

In a multicenter randomized trial, ipratropium nasal spray 0.03% (42 mcg 3 times daily) and beclomethasone nasal spray (84 mcg twice daily) were evaluated for efficacy and safety alone and in combination versus a vehicle placebo with perennial allergic rhinitis.<sup>220</sup> The study enrolled 533 patients. Efficacy was evaluated by patient and physician assessment of severity and duration of rhinorrhea. Combination therapy was more effective than either agent alone in reducing average severity and duration of rhinorrhea during 4 weeks of treatment. During the first week of treatment, ipratropium had faster onset of action and reduced rhinorrhea more than beclomethasone. Beclomethasone was more effective in reducing the severity of congestion and sneezing than ipratropium nasal spray. Combination therapy and monotherapy showed similar adverse effects.

### *fluticasone propionate (Flonase) versus mometasone (Nasonex)*

In a double-blind, placebo-controlled study, 550 patients with perennial allergic rhinitis were randomized to receive intranasal mometasone 200 mcg, fluticasone 200 mcg, or placebo once daily for 3 months.<sup>221</sup> Both drugs were better than placebo in controlling symptoms and decreasing nasal symptom scores. Reduction from baseline in patient-recorded nasal symptoms ranged from 37% to 63% with mometasone, 39% to 60% with fluticasone, and 22% to 39% with placebo. Physician-evaluated reduction of nasal discharge and congestion was greatest with mometasone, but both drugs showed greater reductions than placebo. The number of symptom-free days during the study was 10 days with mometasone, 11 days with fluticasone, and 4 days with placebo. At the end of the 3-month treatment period, the percentage of patients classified as having complete or marked relief was 69% with mometasone, 60% with fluticasone, and 36% with placebo.

In a prospective, controlled study, 94 patients aged 6 to 12 years were randomized to receive 100 mcg mometasone nasal spray (1 spray/nostril) daily or 100 mcg fluticasone propionate nasal spray (1 spray/nostril) daily for 4 weeks.<sup>222</sup> The patients, with parental assistance as needed, completed the Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ). Physical examinations, nasal smears for eosinophil percent, and nasal-peak expiratory flow rate (nPEFR) tests were performed. Patients' total symptom score (TSS) was the sum of the 8 recorded symptom scores. An independent-sample *t* test was used to compare the rate of improvement in the mean nasal PEFR, the mean PRQLQ score (for each question), and the mean TSS for the 2 groups. Baseline TSS and each symptom score were calculated as the mean of the daily scores during the baseline period of 7 days. Patients in the mometasone group exhibited a significant improvement in their TSS ( $t = -2.65, p < 0.05$ ). A detailed TSS analysis showed mometasone to be more effective for relieving nasal symptoms, whereas fluticasone propionate was more effective for relieving non-nasal symptoms. Patient questionnaire scores suggested a significant reduction in symptoms for both the mometasone ( $t = -7.23, p < 0.01$ ) and fluticasone propionate ( $t = -5.43, p < 0.01$ ) groups.

## META-ANALYSES

A Cochrane review of 18 randomized, controlled trials compared the use of intranasal steroids to placebo or no intervention in patients with chronic rhinosinusitis ( $n=2,738$ ).<sup>223</sup> Fourteen studies included participants with nasal polyps and only 1 study evaluated the benefit in children. In general, available data were heterogenous, limiting conclusions. One study reported no significant difference in

health-related quality of life (HRQoL) as measured by the Rhinosinusitis Outcome Measures 31 (RSOM-31). Another study found no significant difference in disease severity as measured by the Chronic Sinusitis Survey (range, 0 to 100; mean difference [MD], 2.84; 95% CI, -5.02 to 10.7). However, another study did find an improvement in disease severity as measured by proportion of improvement on global symptom score (relative risk [RR], 2.78; 95% CI, 1.76 to 4.4). Regarding symptoms measured by the European Position Paper on Rhinosinusitis (nasal blockage, rhinorrhea, loss of sense of smell, and facial pain/pressure), 2 studies evaluated all 4 symptoms with an average MD from baseline of -0.26 with inhaled corticosteroids compared to placebo (95% CI, -0.37 to -0.15). When only rhinorrhea and nasal blockage were considered, the authors found a MD of -0.31 (95% CI, -0.38 to -0.24; 2 studies). Significant differences were also found in the effect size of the individual symptoms; however, the overall quality of evidence was considered moderate to low. Notably, the authors also found an increased risk in epistaxis (risk ratio [RR], 2.74; 95% CI, 1.88 to 4; 13 studies). No statistically significant difference was found in local irritation. No studies provided meaningful data regarding the risk of osteoporosis or stunted growth in children. The authors concluded that there was little information regarding the effect of intranasal corticosteroids on quality of life and moderate- to low-quality data on disease severity impact.

A second Cochrane review of 9 randomized, controlled trials assessed the comparative efficacy of intranasal steroids (n=911). No studies evaluated disease-specific HRQoL.<sup>224</sup> Regarding studies comparing fluticasone propionate to beclomethasone dipropionate, no numerical data were sufficient to find differences in 2 small studies. Regarding studies comparing fluticasone propionate to mometasone furoate, no numerical data were sufficient to find a difference in 1 study. Five studies compared low versus high dose corticosteroids (3 mometasone furoate, 2 fluticasone propionate) reporting greater improvement in nasal polyp score with high-dose intranasal corticosteroids; however, the improvements were small in size and may not be clinically significant. Likewise, epistaxis (defined broadly across studies) was more common in those treated with high-dose intranasal corticosteroid (RR, 2.06; 95% CI, 1.2 to 3.54). The authors concluded that there was no sufficient evidence to suggest that any 1 intranasal corticosteroid is superior to another for the treatment of chronic rhinitis.

## SUMMARY

With the exception of systemic corticosteroids, intranasal corticosteroids are the most effective single agents for controlling the spectrum of allergic rhinitis symptoms, according to the American Academy of Allergy, Asthma and Immunology (AAAAI), American Academy of Otolaryngology – Head and Neck Surgery, and the Institute for Clinical Systems Improvement (ICSI). Intranasal corticosteroids are generally not associated with systemic adverse effects in adults. Local adverse effects, such as nasal irritation and bleeding, may occur, but incidence is minimized if patients are carefully instructed in the use of drugs in this class. The nasal septum should be periodically examined to assure that there are no mucosal erosions that may precede development of nasal septal perforations, a complication rarely associated with intranasal corticosteroids.

Clinical trials have shown intranasal corticosteroids are similar in efficacy. Differences among products include the number of sprays needed per day and dosing frequency. Patient preference for products may also differ.

The intranasal antihistamines, azelastine (Astepro, combination Dymista) and olopatadine (Patanase), offer an alternative to intranasal corticosteroids, oral antihistamines, and intranasal ipratropium for

treatment of allergic rhinitis. Factors limiting use of intranasal azelastine and olopatadine include route of administration and taste perversion.

Ipratropium nasal spray (Atrovent) is safe and effective for treatment of rhinorrhea associated with perennial allergic rhinitis and the common cold. The primary indication for the agent is treatment of patients with nonallergic perennial allergic rhinitis with rhinorrhea as the predominant symptom.

Ticanase (fluticasone propionate) is co-packaged with saline nasal spray. Triamcinolone nasal spray (Nasacort Allergy 24HR), fluticasone furoate (Flonase Sensimist Allergy Relief), fluticasone propionate nasal spray (Flonase Allergy Relief), and budesonide nasal spray (Rhinocort Allergy) are available without a prescription.

Other therapies available include hypromellose (Alzair) which provides a gel-like barrier against air borne allergens and may be used as primary or adjunctive therapy in allergic rhinitis. Additionally, mometasone (Sinuva) a corticosteroid-eluting agent is approved for use in adult patients with nasal polyps.

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